REMARKS

Please note that the claims pending at the time of this filing are the claims of the international application serial no. PCT/GB00/03568, *i.e.* claims 1-33. Claim 33 has been cancelled and claims 34-41 have been added. The pending claims have been amended above to better conform to United States practice. The marked-up version of the changes to the specification and claims are attached hereto in the "Version With Markings to Show Changes Made".

It is respectively submitted that this application is now in condition for substantive examination, which action is respectfully requested.

Respectfully submitted,

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Susan E. Freedman
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims have been amended as follows:

2. (Amended) [An] The E2NT dimer protein [according to] of Claim 1 wherein the residues lie on opposite sides of an N-terminal domain.

3. (Amended) [An] The E2NT dimer protein [according to either preceding claim] of Claim 1, wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer.

4. (Amended) [An] The E2NT dimer protein [according to] of Claim 3 comprising three clusters.

5. (Amended) [An] The E2NT dimer protein [according to either of Claims] of Claim 3 [or 4] wherein a first cluster of vital residues is associated with interactions between N1 and N2 domains and comprises any one or more of the following residues: Ile82, Glu90, Trp92, Lys112, Tyrl38, Val145.

6. (Amended) [An] The E2NT dimer protein [according to any one of Claims 3-5] of Claim 3, wherein a second cluster of residues is associated with N1 interactions and comprises either or both of residues Trp33 and Leu94.

7. (Amended) [An] The E2NT dimer protein [according to any one of Claims 3-6] of Claim 3, wherein a third cluster of residues is associated with N2 interactions and comprises any one or more of the following residues: Prol06, Lysl11, Phel68, Trpl34.

8. (Amended) [An] The E2NT dimer protein [according to any preceding claim] of Claim 1, further comprising residues associated with transactivation and/or replication properties of E2.

9. (Amended) [An] The E2NT dimer [according to] of Claim 8, wherein the residues comprise any one or more of the following residues: Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69.

10. (Amended) [Use of a] A method for determining the structure of a crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein, [according to any preceding claim or homologue thereof in mapping mutations] wherein the E2NT dimer protein and any of its mutations are mapped onto an E2 three-dimensional structure so as to identify areas of amino acid conservation and the effect of mutations on folding of the E2 protein.

11. (Amended) [Use] The method according to Claim 10 in rationalised antiviral drug design.

12. (Amended) [An *in vitro*] A method for identifying and/or selecting a candidate therapeutic agent, the method comprising:

determining interaction of a E2 N-terminal module (E2NT) dimer in a sample by contacting said sample with said candidate therapeutic agent and measuring DNA loop formation in E2 *in vitro*.

13. (Amended) [Use of the] The method according to Claim 12 [in] further comprising identifying and/or selecting an antiviral candidate therapeutic agent.

14. (Amended) [Use according to] The method according to Claim 13, wherein [identification/selection] the identifying and/or selecting of the antiviral candidate therapeutic agent depends on its ability to interfere with or block interactions of E2NT so as to interfere or block viral and/or cellular transcription factors.

15. (Amended) [Use of an E2NT dimerisation inhibitor for the preparation of a medicament for treatment of conditions that arise as a result of] A method of treating an HPV infection in a subject comprising:

introducing an E2NT dimerisation inhibitor in said subject.

16. (Amended) [Use] The method according to Claim 15 [for the treatment of] further comprising treating warts, proliferative skin lesions and/or cervical cancer.

18. (Amended) Use of a dimerisation surface of an crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof according to [any one of Claims 1-9] Claim 1 as a target site for interaction with putative antiviral agents and/or for measuring efficacy of said agents.

20. (Amended) [A] The method of claim 19, wherein the method by which the E2NT crystal structure is obtainable comprises crystallisation using hanging-drop vapour diffusion.

21. (Amended) [A] The method of claim 19, [or claim 20] wherein the method by which E2NT crystal structure is obtainable comprises X-ray diffraction using uranium acetate and gold cyanide E2NT derivatives and refining with data extending to 1.9 Å spacing.

22. (Amended) [A] The method of [any of claims] Claim 19 [to 21], wherein the crystal structure comprises the portions of amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94.

23. (Amended) [A] The method of [any of claims] Claim 19 [to 22], wherein the rationalised drug design comprises designing drugs which interact with the dimerisation surface of E2NT.

32. (Amended) A method for evaluating the ability of a chemical entity to associate with a molecule or molecular complex [according to claim 27 or claim 28] comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3 or a homologue of said molecule or

molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

a. employing computational means to perform a fitting operation between the chemical entity and a dimerisation surface of the molecule or molecular complex; and

b. analysing the results of said fitting operation to quantify the association between the chemical entity and the dimerisation surface.

Claim 33 has been canceled without prejudice or disclaimer.